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An overview of basic molecular biology of SARS-CoV-2 and current COVID-19 prevention strategies

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) manifests as extreme acute respiratory conditions caused by a novel beta coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which is reported to be the seventh coronavirus to infect humans. Like other SARS-CoVs it has a large positive-stranded RNA genome. But, specific furin site in the spike protein, mutation prone and phylogenetically mess open reading frame1ab (Orf1ab) separates SARS-CoV-2 from other RNA viruses. Since the outbreak (February–March 2020), researchers, scientists, and medical professionals are inspecting all possible facts and aspects including its replication, detection, and prevention strategies. This led to the prompt identification of its basic biology, genome characterization, structural and expression based functional information of proteins, and utilization of this information in optimizing strategies to prevent its spread. This review summarizes the recent updates on the basic molecular biology of SARS-CoV-2 and prevention strategies undertaken worldwide to tackle COVID-19. This recent information can be implemented for the development and designing of therapeutics against SARS-CoV-2.

1. Introduction

Severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are the two known lethal coronaviruses that were in news worldwide (Hui et al., 2004a; Zyouf, 2016). In December 2019, the local health center of Wuhan, Hubei Province, China reported that a group of people was suffering from severe pneumonia and the cause was unknown to the health center (She et al., 2020). The expert from Centers for Disease Control (CDC) identified the disease to be a new, and described it as novel coronavirus causing pneumonia (Wu et al., 2020). So, initially World Health Organization (WHO) named the virus as a novel coronavirus (2019-CoV). Based on phylogenetic studies of related coronaviruses, the Coronavirus Study Group (CSG) of the International Committee on Virus Taxonomy renamed the virus as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to similarity with the one that caused the SARS outbreak (SARS-CoVs), and thus named the disease as Coronavirus Disease 2019 (COVID-19) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses,

2020). The rapid increase case of COVID-19 which was characterized by dry cough, high body temperature, breathe shortness, and pneumonia, led the researchers to look into its epidemiology and transmission (Chen et al., 2020a). Three forms of transmission have been recorded so far: a) Symptomatic transmission with symptoms varying from mild (fever and dry cough), severe (shortness of breath, frequency of respiration greater than equal to 30/min, blood oxygen saturation of less than equal to 93%, lung infiltrates of greater than 50% in 24–48 h) (Adams et al., 2020) or critical (septic shock, respiratory failure or multiple organ failure) (Read et al., 2020); b) Presymptomatic transmission (transmission of the virus from infected COVID-19 patients before significant symptoms occur (WHO, 2020; Wei et al., 2020); and c) asymptomatic transmission (transmission of the virus from individuals who do not develop symptoms) (Kimball et al., 2020). Later two forms may fail proper diagnosis as individuals may step out in the crowd assuming the absence of the virus in their body, thus having the potential of spreading COVID-19 silently. To confirm airborne transmission of SARS-CoV, a study was conducted in 2013 that reexamined all confirmed cases and reported the airborne mode of transmission (Read et al., 2020; Yu et al., 2014).

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MARS-CoV, Middle East Respiratory Syndrome Coronavirus; COVID-19, Coronavirus Diseases 2019; AEC2, angiotensin-converting enzyme 2; CD4 and CD8, cluster of differentiation; GM-CSF, macrophage colony-stimulating factor; HCV, hepatitis C virus; HIV, human immune deficiency virus; LAMP, loop mediated isothermal amplification; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention.

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Similarly, a group of researchers analysed 30 aerosol samples from two designated hospital and public areas of Wuhan, and found the RNA load of SARS-CoV-2 to be elevated at patient's toilet areas as compared to isolation wards and ventilated patient's room indicating that SARS-CoV-2 may also hold the aerosol transmission potential (Liu et al., 2020).

SARS-CoV-2 belongs to beta coronavirus and COVID-19 is the third zoonotic outbreak of beta-CoVs (Wang et al., 2020a). The first outbreak was due to SARS-CoV, which was originated from bat and civet cat occurred during 2002–2003 and second was MERS-CoV, which began in Saudi Arabia with approximately 2500 cases, 800 deaths and still counting (Wang et al., 2020a; Civljak et al., 2020). Structurally, SARS-CoV-2 has round or elliptic and often pleomorphic form, with a diameter of approximately 60–140 nm and is sensitive to ultraviolet rays and heat (Yu et al., 2014). The complete structure consists of mainly four components: spike (S), nucleocapsid (N), membrane (M), and envelop (E) (Fig. 1) (Cascella et al., 2020). The most possible animal reservoir hosts are believed to be wild animal and bats (Zhou et al., 2020), but yet no confirmation have been attained about its direct transmission through bat or wild animals or some other intermediates (Perlman, 2020). The whole-genome analysis of SARS-CoV-2 showed that it has 96% similarity with bat coronavirus, indicating that bat might be the most possible host of SARS-CoV-2 (Ji et al., 2020a). But based on metagenomics, molecular biology detection, and electron microscopy, SARS-CoV-2 isolated from pangolins also show 99% similarity with pandemic causing human viral strain suggesting pangolins may also be the possible potential host of SARS-CoV-2 (Zhang et al., 2020a). Therefore, potential intermediate host of SARS-CoV-2 still remains unclear. Moreover, mutation prone nature of this novel virus has remain the prime reason for its global spread and severity (Khailany et al., 2020; Ray, 2020).

Coronaviruses are enveloped, positive-sense, single-stranded RNA virus with 3' and 5' cap structure. The approximate genome size is 30 kb in length (Kumar et al., 2020c). Based on the genome structure and expression of the family Coronaviridae, it is divided into four genera (alfa, beta, gamma, and delta) coronavirus (Woo et al., 2012). Alpha-coronavirus and betacoronavirus infect mammals and show similarity to

other positive-sense, single-stranded RNA virus. In this review, we intend to summarize the current molecular biology of SARS-CoV-2 including its basic biology inside the host, genome organization, expression, and enzymes involved in the replication. Recent advances in prevention and control strategies across the globe have also been summarized.

2. Genome arrangement

Many notable features of the SARS-CoV-2 and its full-length genome, based on experiment and comparison with SARS-CoV and related coronaviruses have been elucidated (Mariano et al., 2020; Zhou et al., 2020; Wan et al., 2020; Andersen et al., 2020). The genome sequence of SARS-CoV-2 was found to have similar organization as that of CoVs (Khailany et al., 2020). It consists of approximately 29,903 nucleotides, linear ssRNA holding 14 open reading frames (Orfs). Positions of the untranslated regions, structural genes and reading frames in the genome are detected as: 5'UTR region (1 to 265)nt, Orf1ab (266 to 21,555)nt, Orf3a (25,393 to 26,220)nt, E (26,245 to 26,572)nt, M (26,523 to 27,191)nt, Orf6 (27,202 to 27,387)nt, Orf7a (27,394 to 27,759)nt, Orf7b (27,756 to 27,887)nt, Orf8 (27,894 to 28,259)nt, N (28,274 to 29,533)nt, Orf10 (29,558 to 29,674)nt and 3'UTR (29,675 to 29,903)nt (Fig. 2A). Single Orf8, and additional Orf9b and Orf9c were revealed recently in the genome of SARS-CoV-2 (Gordon et al., 2020). It also contains a 5' cap, Orf1ab, replicase gene, S (spike Orf), E (envelop Orf), M (membrane Orf), N (nucleocapsid Orf), and a 3' poly-A tail (Mousavizadeh and Ghasemi, 2020; Paules et al., 2020; Shereen et al., 2020; Khailany et al., 2020). The proteins encoded by the S, E, M, and N gene represent the structural proteins (Gordon et al., 2020; Fehr and Perlman, 2015), and the proteins encoded by the Orf3a, Orf3b, Orf6, Orf7a, Orf7b, Orf8, Orf9b, Orf9c, and Orf10 in SARS-CoV-2 represents the accessory proteins, which provides a collective advantage in infection and pathogenesis (Gordon et al., 2020; Li et al., 2005; Lan et al., 2020).

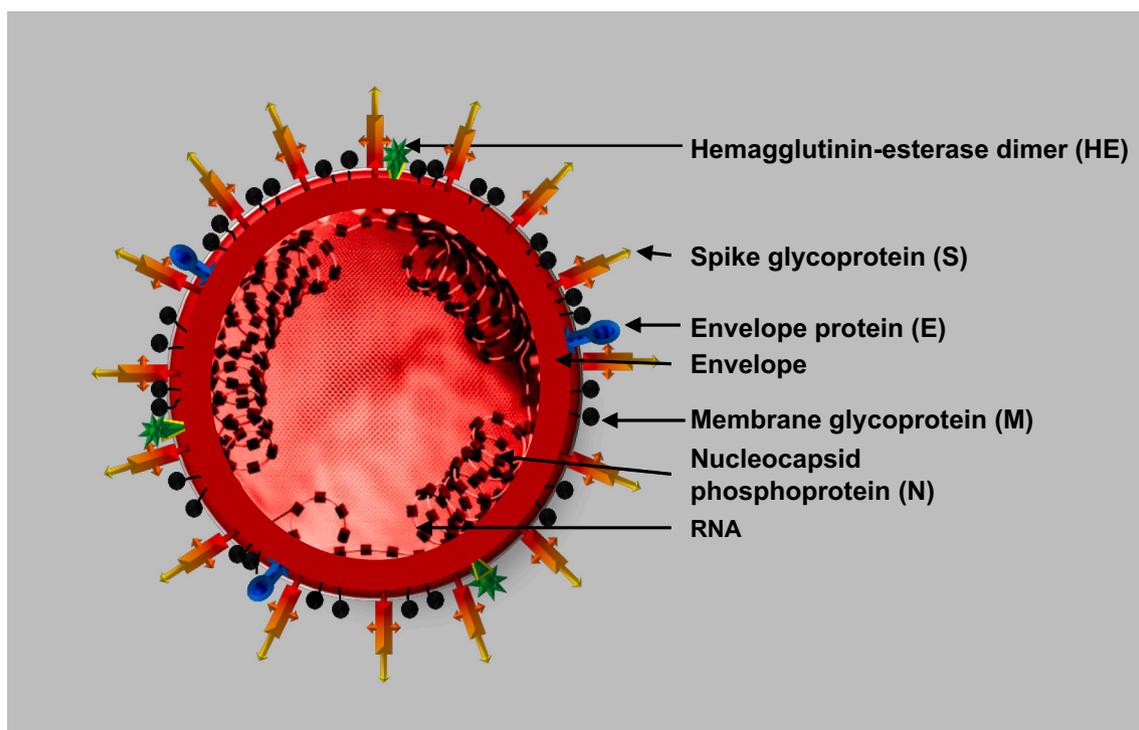


Fig. 1. Structure of SARS-CoV-2.

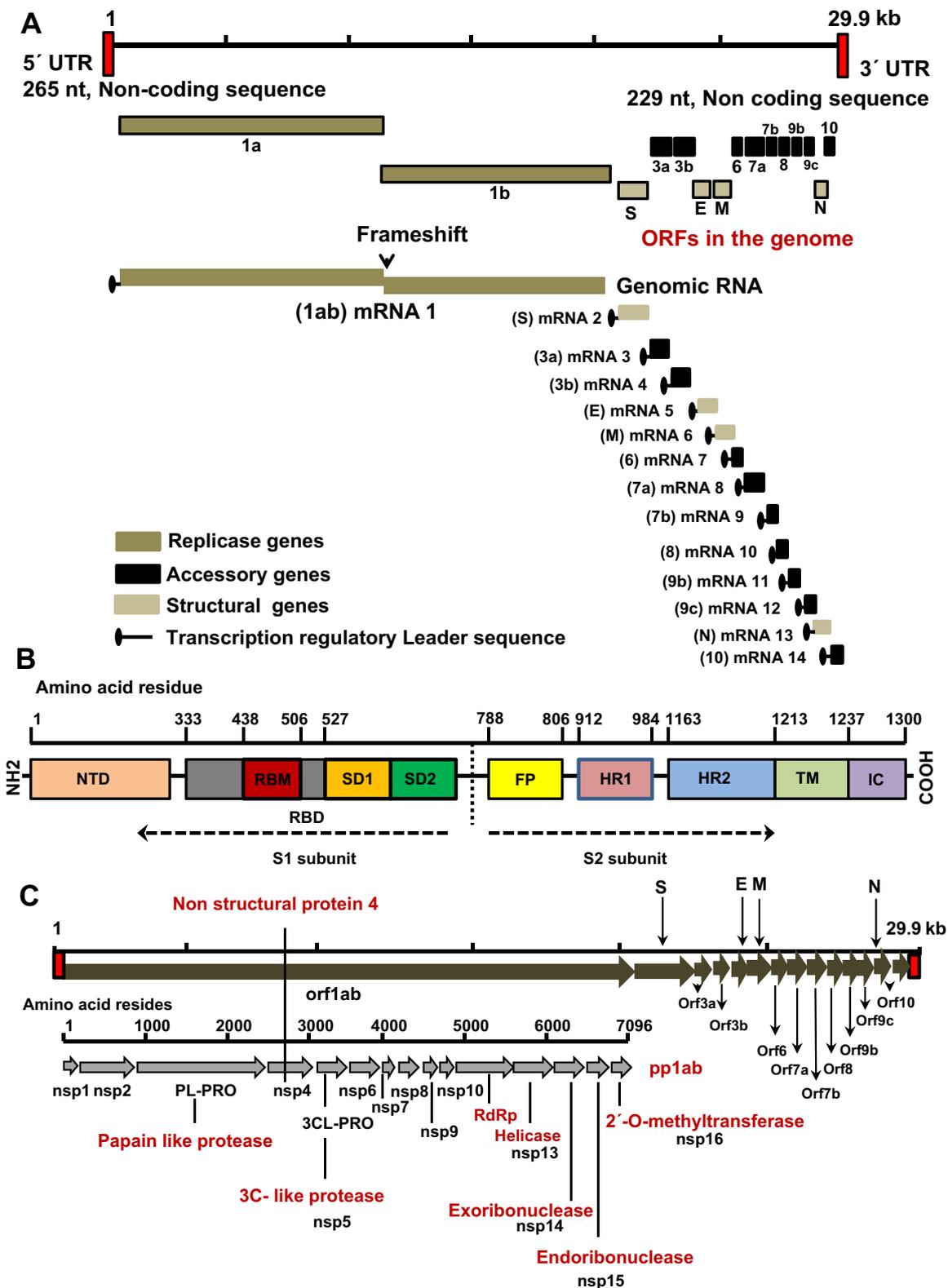


Fig. 2. A) Genome organization and RNA synthesis of SARS-CoV-2. The replicase gene comprises of ORF 1a and 1b which are required for the replication of the genome and the synthesis of sgRNAs. The structural genes, Accessory genes in the genome and leader sequence derived from 5 prime end of the genome are depicted. B) Structure of SARS-CoV-2 spike protein. Spike protein of 1300 amino acid with NTD, N terminal domain; RBD, receptor binding domain, RBM, receptor binding motif; SD1, subdomain 1; SD2, subdomain 2 are the components of S1 subunit, Left side (can be divided into S1A, S1B and S1C/D) and FP, fusion peptide; HR1, heptad repeat 1; HR2, heptad repeat 2; TM, transmembrane region; IC, intracellular domain are the components of S2 subunit, right side. C) Overview of proteolytic processing of SARS-CoV-2. Replicase polyprotein pp1ab (740–810 kDa) which gets processed into nonstructural proteins (nsps). The 3C-like protease (3CL-PRO, marked in red) in SARS-CoV-2, may be responsible for cleaving the C-terminus of replicase polyprotein. The polyproteins are processed by papain like protease (presented in red). RNA-dependent RNA polymerase (RdRp), responsible for viral genome replication and transcription is indicated in red color.

3. Receptors

SARS-CoV-2 entry into the host cell is mediated by the special spike protein, which is composed of three domains, the outer N-terminal domain having unit S1 and S2, the cytoplasmic C-terminal domain, and a transmembrane domain (Lan et al., 2020; Ziebuhr, 2004) (Fig. 2B). S1 and S2 are highly conserved and are glycosylated. Priming of S protein by cellular proteases (Transmembrane protease, serine 2, TMPRSS2) results in the cleavage at a specific site and S2 subsequently mediates the fusion of viral and host membrane (Hoffmann et al., 2020a). A receptor-binding domain (RBD) presents in the spike protein precisely binds to the angiotensin-converting enzyme 2 (ACE2) present in the host membrane (Li, 2016; Li et al., 2003). The binding nature was revealed upon determination of the crystal structure of the RBD domain bound to ACE2 at 2.45 Å resolutions, which showed that the binding mode SARS-CoV-2 is nearly identical to SARS-CoV RBD (Lan et al., 2020). But a functional polybasic (furin) in SARS-CoV-2 is optimized to effectively bind to ACE2, indicating stronger infectivity (Andersen et al., 2020). The special cleavage site was absent in the earlier SARS-like CoVs (Coutard et al., 2020). A computational analysis predicted that a single N501T mutation may lead to an increased binding affinity of SARS-CoV-2 RBD and ACE2 present in the human cell (Wan et al., 2020). The same research group also described the similarity (73.8–74.9% amino acid) of the predicted structure of the spike RBD with the crystal structure of the spike RBD of SARS-CoV (PDB 2GHV) complexed with human ACE2. Moreover, determination of the crystal structure of the RBD revealed the compact human angiotensin-converting enzyme (hACE2) binding ridge in SARS-CoV-2 RBD which stabilizes the binding of two viruses and increases the hACE2 binding affinity. This may be the reason of animal to human transmission (Shang et al., 2020). Recently, the full-length structure of S-protein has been revealed, but as a mixture of pre-fusion and post-fusion forms (Cai et al., 2020). Additionally, cryo-ET in combination with molecular dynamics was utilized to trace the rearrangement and conformational change at molecular level of S protein from pre to post fusion (Turoňová et al., 2020). Thus, opens up opportunities to explore structure-based drugs which targets during viral fusion to human cell membrane. Interestingly, a group of scientists recovered a mutant strain (Del-mut-1, 10 amino acid) in S1/S2 junction from Vero-E6 cells which did not show any major change in lung pathology and hence could be a lead for attenuated vaccines (Lau et al., 2020). Also, protease inhibitor targeting the furin and TMPRSS2 activity have shown positive results in inhibiting SARS-CoV-2 and may be promising in the therapeutics field (Bestle et al., 2020; Hoffmann et al., 2020b).

4. Genome expression

The viral genome entry into the host cytoplasm is facilitated by S protein, which is the translation product of 1273 amino acids encoded by S gene. It mediates the fusion of envelope with the host's cell membrane (Song et al., 2018). The product encoded by Orf1a is polyprotein 1a (pp1a, 4405 amino acid residue). Addition of 1b encoded sequence to 1a, yield 7096 amino acid residue protein (pp1ab) which occurs as a result of ribosomal shifting of 1 reading frame (Wu et al., 2020b). Thus, Orf1ab encodes a huge replicase polyprotein. The four structural genes S, E, M, and N encodes the Spike protein (1273 amino acid), Envelope protein (75 amino acid), Membrane protein (222 amino acid), and Nucleocapsid phosphoprotein (419 amino acid) respectively. These four structural proteins in SARS-CoV-2 have been identified and characterized, where Envelope (E) and Membrane (M) protein are found to be involved in virus packing, and spike glycoprotein (S) in viral entry (Shang et al., 2020; Ye et al., 2020; Mariano et al., 2020). The Nucleocapsid (N) protein is involved in RNA binding and packaging (Mariano et al., 2020). Except spike protein, very limited structural information on the other structural proteins are available yet. N protein in SARS-CoV-2 is believed to play role during genome replication (Cong et al., 2020). An identical leader sequence (protein of 180 amino acids) is

carried by each mRNA (Kumar et al., 2020c; Hoffmann et al., 2020a; Li, 2016). Orfs of SARS-CoV-2 have been validated and structural information of 9 accessory proteins have been discussed till date (Mariano et al., 2020; Khailany et al., 2020; Wu et al., 2020b) (Fig. 2A). SARS-CoV-2 encodes Orf10 in the genome terminal which was absent in SARS-CoVs and related strains, and a single Orf8 is found instead of Orf8a and Orf8b (Nguyen et al., 2020). The cryo-EM structure of Orf3a revealed a unique fold structure harboring a channel which is joined to the cytoplasm (Kern et al., 2020). Not much information of Orf7a and Orf9b in SARS-CoV-2 is available yet, but they are believed to play a similar role as in SARS-CoV (Meier et al., 2006; Taylor et al., 2015). SARS-CoV-2 Orf8 was resolved based on homology model to Orf7a, and it was found to interfere with major histocompatibility complex-1 (MHC-1) and inhibit presentation to the immune cells and interferon signaling in the host cell (Zhang et al., 2020c; Li et al., 2020a). Similarly, Orf3b and Orf6 are also reported to be involved in downregulation of Interferon (IFN-1) signaling (Konno et al., 2020; Yuen et al., 2020). Thus, interferes with the human immune system. A recent study suggested the internal modification sites concerning the poly (A) tail of the transcript of Orf1ab and S which are predicted to play a crucial role in RNA stability inside the host (Kim et al., 2020a). Due to the complex regulation of viral RNA synthesis and quick recombination, SARS-CoV-2 may show flexibility in specificity and sensitivity.

5. Proteins involved in genome replication and transcription

Unlike other RNA viruses, CoVs including SARS-CoV-2 have the largest RNA genome which gets translated into structural and non-structural proteins (nsps) (Lai and Stohlman, 1981; Mousavizadeh and Ghasemi, 2020). These non-structural proteins co-operately involve in the replication of SARS-CoV-2 genome (Mousavizadeh and Ghasemi, 2020). Complex polyproteins of SARS-CoV-2 and other coronaviruses are due to the construction of diverse RNA sequences with varied enzymatic activities. The nsps undergo post-translational changes and regulate the activities of the replicative proteins (Fehr and Perlman, 2015). Orf1a produces pp1a (440–500 kDa) which gets processed into 11nsps and ribosomal frameshift results in the continuation of translation of Orf1b producing a huge polypeptide pp1ab (740–810 kDa) which gets processed into 16 nsps (Kim et al., 2020a) (Fig. 2C). The 16 nsps encoded by Orf1ab are directly involved in the infection cycle inside the host (Gordon et al., 2020). A study reported an extra N-terminal hairpin motif in SARS-CoV-2 nsp12, which was absent in earlier SARS-CoV (Gao et al., 2020). Earlier coronaviruses including SARS-CoV possess a papain-like protease for the processing of polyproteins (Thiel et al., 2003). But a genome-wide structure and functional modeling by Zhang lab, University of Michigan revealed an additional 3C-like protease (3CL-PRO) in SARS-CoV-2, which may be responsible for cleaving the C-terminus of replicase polyprotein and recognizes substrate containing sequence ILMVF-Q-I-SGACNN and also can bind an ADP-ribose-1-phosphate (Zhang Lab, 2020). Nsp1 structure in complex with ribosomes was revealed in SARS-CoV-2, and reported to play a significant role during infection (Thoms et al., 2020; Schubert et al., 2020). Not much information is yet known about SARS-CoV-2 nsp2, however it is believed that, it may contribute to the infectivity of the virus (Angeletti et al., 2020). Determination of the structure of papain-like protease (deposited in PDB), have revealed a homotrimeric fold, which is also found to be conserved in SARS-CoV and MERS CoV and is clearly involved in cleavage activity (Fu et al., 2020). The structural similarity of SARS-CoV-2 papain-like protease to SARS-CoV-2 has led researchers to explore drug development and several inhibitors (Fu et al., 2020; Rut et al., 2020). Huang and his team also demonstrated de novo designing of peptide that blocks the interaction between SARS-CoV-2 spike and human ACE2 (Huang et al., 2020). Structurally, nsp3 harbors two ubiquitin-like domain, where domain 1 may interact with ssRNA and N protein (Cong et al., 2020). However, the role of nsp3 domain 2 is still unclear in SARS-CoV-2. The nsp5 together with the papain-like protease

forms the main protease that is reported to be involved in Orf1ab cleavage (Mousavizadeh and Ghasemi, 2020).

Replication and transcription of the viral genomic RNA is carried out mainly by nsp12 possessing RNA-dependent RNA polymerase (RdRp) activity (Snijder et al., 2016). The cryo-EM structure of the complex nsp12-nsp7-nsp8 at 2.9-Å and N terminal beta-hairpin domain have been resolved (Gao et al., 2020). The complete structure, almost all residues is revealed, where residues 4 to 28 and 51 to 249 include 8 helices and 5-stranded beta-sheet respectively towards the N terminus. The three conserved structure of the polymerase viz. finger domain (L366-A581), palm domain (T582-P620 and T680-Q815), and a thumb domain (H816-E920) are also shown where palm domain forms the active site of the enzyme (Gao et al., 2020). Recently, it has been found that substitution of amino acids in nsp7-8-12 peptide of SARS-CoV-2 have resulted in the decrease activity of RdRp and stability of the proteins (Peng et al., 2020). Hence, RdRp remains a potent candidate for drug target (Yin et al., 2020). The information revealed regarding the structural rearrangement of nsp7-nsp8 and its association with the regulatory role and activity of the polymerase could be utilized towards designing targets for future therapeutics (Shi et al., 2020a). SARS-CoV nsp13 helicase is considered to be a multi-functional protein harboring a zing-binding domain in N-terminus showing RNA and DNA duplex-unwinding activities (5'-3') (Vanov et al., 2004). The structure of SARS-CoV-2 nsp13 helicase coupled with the core RdRp has been revealed and interaction was detected with nsp7-8-12 (Chen et al., 2020b). The structure of nsp10-16 complex has been determined in SARS-CoV-2 and found to be highly similar to SARS-CoV and MERS CoV (Rosas-Lemus et al., 2020). The structure of nsp14 however in SARS-CoV-2 has not yet been resolved. The proof-reading activity of nsp13-RdRp complex was suggested initially in SARS-CoV-2 (Chen et al., 2020b), despite the structural analysis of the complex, its physiological role still remains unknown. Nsp15 is uridylylate-specific Endoribonuclease (NendoU) harbor uridylylate specific enzyme in the presence of Mn²⁺, 2'-O-methylase is predicted to mediate mRNA cap 2'-O-ribose methylation to the 5'-cap of viral mRNA (Zhang Lab, 2020). SARS-CoV-2 nsp15 is found to be conserved in SARS-CoV and MERS CoV (Zhang et al., 2018; Kim et al., 2020b). Nsp9 in SARS-CoV-2 is shown to be in dimeric form (Littler et al., 2020), and in other CoVs it was found to be involved in viral replication (Miknis et al., 2009). A recent study reported the structure of nsp10-16 complex and its structural similarity to SARS-CoV and MERS CoV, indicating its probable conserved function (Rosas-Lemus et al., 2020). Nsp10 can additionally interact with nsp14 to aids the exonuclease activity. Moreover, nsp10 is known to have multiple function during RNA capping (Chen et al., 2009). SARS-CoV-2 ExoN has been predicted to be involved in repair mechanisms (Snijder et al., 2016).

6. Viral entry and host immune responses

The entry process of 2019 coronavirus (SARS-CoV-2) follows the usual pattern of a common virus life cycle, which starts with the attachment of the spike protein with the host ACE2 receptor. The cellular Human Airway-Trypsin like protease (HAT), cathepsins, and Transmembrane protease serine 2 (TMPRSS2) breaks the S-protein and facilitate the fusion of cellular and viral membrane and release of SARS-CoV-2 genetic material RNA inside the host cell takes place (Glowacka et al., 2011; Walls et al., 2000; Shereen et al., 2020). Apart from TMPRSS2, few others genes including BSG were recently studied for genetic variation in 131 COVID-19 positive patients and showed that host genes variation may be associated with severity and susceptibility of infection. (Latini et al., 2020). The receptor-binding region (RBD) of SARS-CoV-2 uses the hACE2 receptor as an entry key (Wan et al., 2020). The replicate gene of the genomic RNA of the virions, once inside the host cell cytoplasm, is translated using host cell machinery. After the formation of nsp by proteolytic cleavage, some of the nsp combine with the sense strand (RNA+) to form the replicase transcriptase complex

which facilitates RNA replication. When RNA+ strand is replicated, it produces genomic RNA but that happens to be antisense RNA (RNA-). The antisense RNA strand can be replicated back into the genomic (RNA+) strand or can be transcribed into sub-genomic RNAs by discontinuous transcription (Brown, 2007). The sub-genomic RNAs are mRNAs that can be translated into viral structural proteins. Many different structures have been proposed which regulate alternate RNA synthesis stages which including seven stem-loop structures at the 5'-UTR (Guan et al., 2011; Lee et al., 2011; Raman et al., 2003; Liu et al., 2011); a bulged stem-loop, a pseudoknot, and a hypervariable region at the 3'-UTR (Goebel et al., 2007; Williams et al., 1999; Hsue and Masters, 1997; Krijnse-Locker et al., 1994). CoVs genomic RNA replication is mediated by RNA-directed RNA polymerase (Pol/RdRp) which is also responsible for transcription of the viral RNA genome. There is experimental evidence for SARS-CoV that nsp7 and nsp8 activate and confer processivity to the RNA-synthesizing activity of the polymerase (Walls et al., 2000). The synthesis of sub-genomic RNA through the discontinuous extension of the antisense RNA strand is mediated by the fusion of leader transcription regulating sequences (TRS) and body TRS. It has been found that Pol/RdRp when reaches at any one of the body TRS, it pauses and then either continues elongation to the next TRS or jumps to the leader TRS, thus terminating transcription (Wan et al., 2020). Following the formation of sub-genomic and genomic RNAs, the viral structural proteins encoded by the sub-genomic RNAs are translated. These proteins are then trafficked to the Endoplasmic Reticulum followed by the entry into the Golgi Intermediate Compartment via the secretory pathway. The viral genomes are encapsulated by the N-protein into the membranes of the ER-Golgi intermediate compartment (ERGIC) where both the structural proteins and viral genome form mature virus particles (Tooze et al., 1984; Bos et al., 1996). Both the M and E proteins function together to form the coronavirus envelopes (Bos et al., 1996). Finally, the mature virions transported via vesicles and released out of the cell through exocytosis.

While the virus completes its life cycle in the host cell, the signaling molecules of the host immune system already starts its action either by regulating the expression of the genes associated with immune response or by initiating cascade of reactions necessary for immune response. SARS-CoV-2 affect CD4⁺ and CD8⁺ T cells of the host resulting in a smaller number of IFN production (Chen et al., 2020c). In humans, after cell infection, the up-regulation of Interferon stimulated genes (ISGs) is necessary for the induction of Interferons for antiviral defense (Deek et al., 2017). The binding of the transcription factor signal transducer and activator of transcription factor 1 (STAT1) homodimers to ISGs are moderated by the various IFNs (IFN α , IFN β , IFN γ , and IFN λ) and thus, play a crucial role in host defense (signaling the nearby cells) (Jewell et al., 2010; Broggi et al., 2020). Recently, it has been suggested that uses of approved IFN in clinical therapy against SARS-CoV-2 may either vanish or worsen the symptoms of COVID-19 (Dong et al., 2020; Lei et al., 2020). A recent finding suggested that mutation in the type I IFN and related genes may be associated with severe pneumonia (Zhang et al., 2020b). Therefore, administration of type I IFN specially in the early stage of SARS-CoV-2 infection in patients may lessen the effect of life-threatening pneumonia. Experimentally it has also been shown that IFN α drives the up-regulation of ISGs in ACE2 expressing cells and high expression of the same in influenza-infected upper epithelial cells (Ziegler et al., 2020). Thus, this information can be considered for designing IFN-system targeted therapeutics. It is clear that upon an attack of coronaviruses, due to the huge activation of immune molecules in the host cell, a cytokine storm is generated which results in adverse damage of both targeted and nearby tissues (Fig. 3) (Cascella et al., 2020; Schett et al., 2020). A study suggested that interleukin 6 (IL-6) which is generated by leukocytes plays a leading role in inducing the storm (Cascella et al., 2020). Moreover, IL6 is known to be associated with inflammatory response, disease, disorders, differentiation of B lymphocytes, cell growth regulation, and more importantly with cytokine release syndrome (CRS) (Yu et al., 2014; Schett et al., 2020). People with

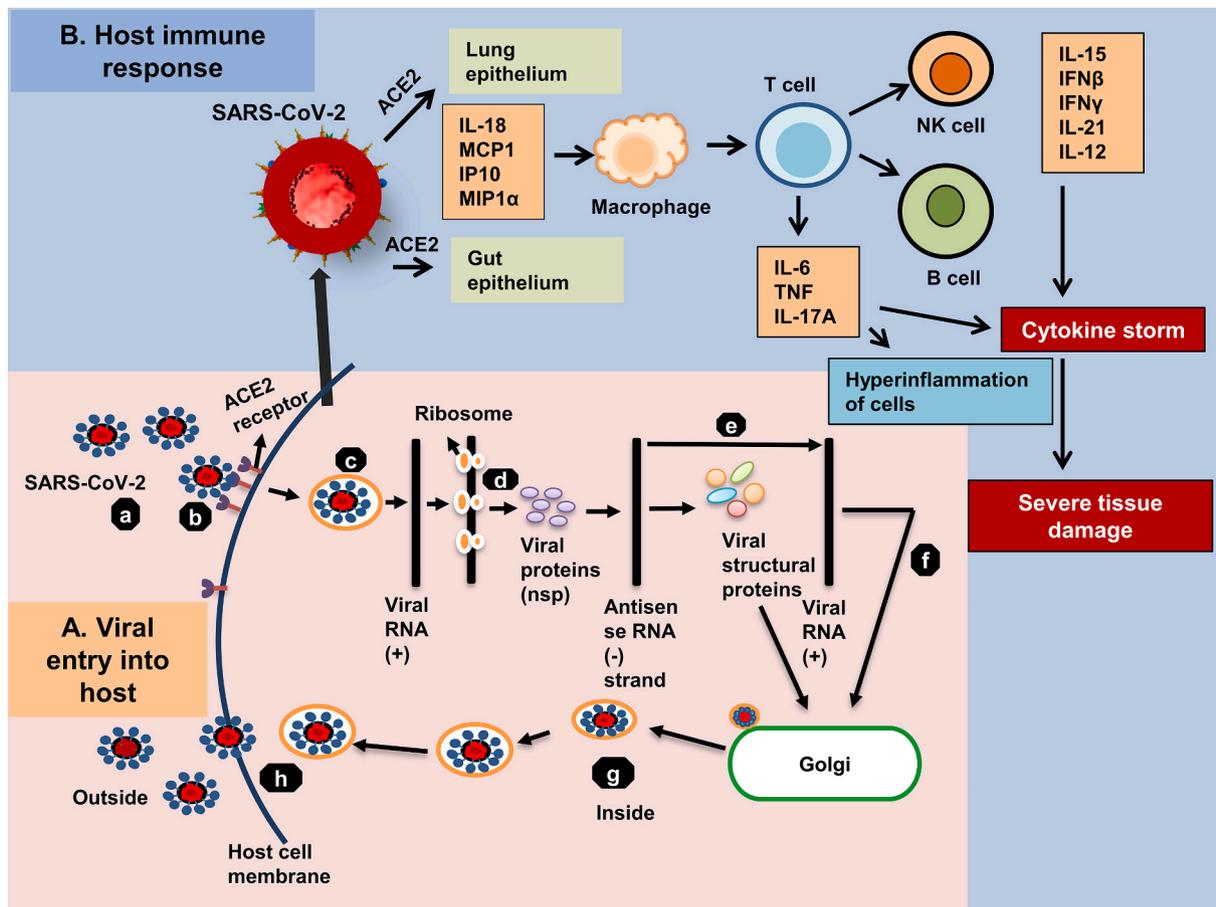


Fig. 3. Overview of viral entry and host immune response leading to cytokine storm and multiple tissue damage; A) SARS-CoV-2 entry, replication, transcription and release outside (indicated within red circle) a. SARS-CoV-2 virus, b. binding of spike protein with ACE2 receptor, c. Endocytosis and release of viral genome into the host cell, d. synthesis of nsp from polyproteins by genome RNA translation using host machinery, e. replication and transcription of antisense RNA (formation of viral structural proteins), f. assembly of the RNA(+) strand and structural proteins into Golgi bodies, g. transport of the mature virus particles to the outside of the cell via vesicles, h. exocytosis and release of SARS-CoV-2 virus; B) Host immune response leads to Cytokine storm in COVID-19 (indicated within blue circle).

diabetes, heart disease, pulmonary disease, and kidney problem when infected with SARS-CoV-2 have shown worse outcomes because of the plasmin and proteases which tend to break the S protein (furin site) which eventually increases its virulence (Ji et al., 2020b). However, this system could be a target for future therapeutics.

7. Techniques in COVID-19 detection

The shortage of first-hand testing kits and the unavailability of reliable and efficient diagnostic tools also elevated the risk of spreading COVID-19 infection. So far, several diagnostic tools were developed to manage the COVID-19 outbreak. Information at the molecular level and the use of molecular biology tools have always been promising in detecting viral diseases (Beilby, 2006). Techniques adopted till date around the world for diagnosis and controls of COVID-19 are summarized:

7.1. Molecular biology-based diagnostic tools

Molecular biology-based diagnostic tools require information regarding the genomic and transcriptomics of the target organism. Comprehending molecular biology not only helps in the detection of such pathogens, but also opens the way to target and combat the same. One such technique is Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) (Corman et al., 2020) which has been used since long in the detection of pathogenic viruses involving in respiratory infection (Poon

et al., 2003; Yam et al., 2003; Hui et al., 2004b). Scientists from different regions adopted various assays of RT-PCR approved by WHO, CDC, and FDA EUA (Hirotsu et al., 2020; Beltran-Pavez et al., 2020; Yelin et al., 2020; Poljak et al., 2020). However, the availability of RT-PCR tools and reagent kits are not up to the demand. Additionally, many reports suggests that though RT-PCR is known for its broad sensitivity (can detect even at low viral load) (Saah and Hoover, 1997), but in clinical practice, the diagnostic sensitivity is 50–70% (Li et al., 2020b; Kelly et al., 2020; Wang et al., 2020b) as false negative results are often being obtained for a single test (Bullis et al., 2020; Xiao et al., 2020). The false negative results may be due to several factors, viz. errors in sample preparation, machine handling, errors in correct interpretation of the results. Moreover, RT-PCR is known for its high specificity (about 99%) (Nalla et al., 2020; Lu et al., 2020), hence, contamination with trace amount of SARS-CoV-2 nucleic acids in the sample may result in false positivity (Stites and Wilen, 2020). Thereby, proper protocol standardization to minimize contamination, optimization and validation is required for increment of accuracy in diagnosis. In addition, viral evolution and time of SARS-CoV-2 test performed (i.e., time of course of infection at which the sample is obtained) are important factors in RT-PCR sensitivity (Cheng et al., 2020; Osório and Correia-Neves, 2020). Isothermal amplification techniques viz. recombinase polymerase amplification (Piepenburg et al., 2006), loop-mediated isothermal amplification (LAMP) (Notomi et al., 2000), Reverse Transcriptase LAMP (RT-LAMP) (Yang et al., 2020; Yu et al., 2020), helicase dependent amplification (Vincent et al., 2004) are in the developmental and clinical stage for SARS-CoV-2 detection. X-

ray and chest CT scan insights better screening and diagnosis and simultaneously lowers the risk of spreading the disease (Narin et al., 2020; Kanne, 2020). Artificial Intelligence techniques can be coupled with a Chest CT scan for safe, efficient, and accurate image acquisition, segmentation, and diagnosis of COVID-19 (Shi et al., 2020b). RNA sensing is possible due to CRISPR-Cas technology that utilizes Cas12 coupled with isothermal amplification and DETECTOR technique (Broughton et al., 2020), and Cas13a/C2c2 proteins (Gootenberg et al., 2017) following Cas13 based detection methodology and SHERLOCK detection protocol (Kellner et al., 2019).

7.2. Host-antibody and viral protein-based diagnosis

One of the common types of rapid diagnosis of COVID-19 is detection of antigens and antibodies (in the blood samples of the individuals that have likely been infected by SARS-CoV-2) (Li et al., 2020c). However, antibodies produced against SARS-CoV-2 may counteract with other pathogens resulting in false-positive detection. Also, several factors such as the severity of the disease, age of the infected individual, and medication may result in hindrance in the actual diagnosis of COVID-19 infection (Che et al., 2005). Similarly, rapid diagnostics using antigens (viral protein) may not provide full-proof diagnostics which may be due to limitations in quality and time of sample collection, concentration of target antigen in the sample, and so forth. In a note of this, uses of antibodies and viral proteins for rapid diagnosis of COVID-19 have not been yet approved by WHO although encouraged scientists and researchers to utilize it in disease surveillance and epidemiologic research (*Advice on the Use of Point-of-Care Immunodiagnostic Tests for COVID-19, 2020; SARS-CoV-2 Diagnostic Pipeline, 2020*). Very recently, first indigenous antibody detection kit (human IgG ELISA test kit) was developed by National Institute of Virology (NIV), Pune which will aid in the surveillance of SARS-CoV-2 infected population (*National Institute of Virology Develops 1st Indigenous ELISA Test Kit for Covid-19: Harsh Varadhan, 2020*).

7.3. Non-laboratory-based diagnosis

Diagnosis at the preliminary level is at most important to estimate as well as minimize the spread of the virus from an infected person to a healthy individual. Though RT-PCR based diagnosis is more accurate, its time-consuming property leads to the need for non-laboratory rapid testing kits. Several pharmaceutical industries and companies have come up with rapid antibody (IgM/IgG) testing kit and Real-time PCR mediated SARS-CoV-2 diagnostic kits. US-FDA and CE have approved several real-time PCR kits and CE marked a rapid antibody test for SARS-CoV-2 diagnosis and can be used directly after due marketing approval from DCGI. CSIR India has come up with low-cost paper-strip test kits that use a cutting-edge-gene-editing tool (CRISPR-Cas9) to target and identify the genome sequences of the novel coronavirus in the samples of suspected individuals within an hour (Choudhary, 2020). As of 1st May 2020, 45 real-time PCR kits (10 are Indian based company) and 23 antibody-based rapid tests (9 from Indian based company) have been validated by ICMR and NIV Pune respectively (*Performance Evaluation of Commercial Kits for Detection of SARS-CoV-2 RNA by Real Time PCR, 2020; Guidance on Rapid Antibody Kits for COVID-19, 2020*).

8. Prevention and control strategies of COVID-19 to date

Research is at its peak to develop an efficient and effective vaccines/drugs considering molecular biology and the genetic makeup of both the virus and host system. Based on approaches undertaken by different countries around the globe, the strategies have been summarized into Western, Homeopathy, and traditional. Certain innovative ways undertaken to prevent the disease from spreading are also summarized.

8.1. Western

Research projects are ongoing for approximately 86 vaccines in the phase of clinical trial and 12 vaccines are approved for emergency around the world (Zimmer et al., 2020; Basta and Moodie, 2021). The first human trial for COVID-19 vaccine mRNA-1273 was carried out by the USA which was developed by the National Institute of Allergy and Infectious Disease (NIAID) scientists and their collaborators at the biotechnology company Moderna, Inc., based in Cambridge (Mishra and Carnahan, 2020). Following that, a series of trials have been carried out emphasizing both host and viral proteins targeting mainly the replication process. (Lee, 2020). The first vaccine mRNA-1273 was designed to target specifically the spike protein to prevent binding with the host receptor ACE2 (Angiotensin-converting enzyme 2) (Fleming, 2020; Daddu, 2020). On the other hand, researchers have also focused on the use of Hydroxychloroquine and Azithromycin, since it raises the pH of the cell leading to decreased enzymatic activity and viral replication. It was also found to resist the effective binding of Spike-ACE2 (Gautret et al., 2020; Schrezenmeier and Dorner, 2020; Wang et al., 2020a; Wang et al., 2020c). Chloroquine and Zinc have similar functions to Hydroxychloroquine and Azithromycin, but Chloroquine serves as a gateway for zinc to diffuse through the cell (Gautret et al., 2020; Schrezenmeier and Dorner, 2020; Matthay et al., 2020; Vincent et al., 2020). Remdesivir (GS-5734), an inhibitor to RNA-dependent RNA polymerase showed promising results against SARS-CoV-2 *in vitro*. As a result, the Food and Drug Administration approved Remdesivir for use against SARS-CoV-2 in adult and paediatric patients aged 12 years and weighing at least 40 kg (Rees, 2020). Additionally, Argentina's scientists discovered that high doses of dexamethasone are effective in treating Acute Respiratory Distress Syndrome caused by SARS-CoV-2 (Maskin et al., 2020).

Moreover, certain companies namely, Moderna, Pfizer-BioNTech, Zydus, Urvac, etc. are working on a vaccine based on genetic approach of passive immunization (Zimmer et al., 2020). Few other companies, CanSinoBio, Gamaleya Research Institute, Johnson and Johnson, AstraZeneca-University of Oxford, etc. are working on viral vector vaccine, where non-replicating viral vectors which carry SARS-CoV-2 genes are used to develop memory based adaptive immune response. Novavax, Medicago, Anhui Zhifei Longcom-Chinese Academy of Medical Sciences, Bektop, etc. developed protein-based vaccine that carries protein of the virus. Wuhan Institute of Biological Products, Sinovac, Indian Council of Medical Research are working on inactivated coronavirus vaccine approach where vaccine carries virus which is either weak or already killed by different chemicals (Zimmer et al., 2020). Besides the companies and institutes mentioned above, Several Institutes such as Murdoch Children's Research Institute, Washington University, India's National Institute for Research in Tuberculosis, The Serum Institute of India, etc. are working on repurposed vaccines; i.e. vaccines which are already in use to treat other diseases with similar symptoms to COVID-19 (Zimmer et al., 2020). Several Pharmaceutical industries also considered drugs namely Arbidol Hydrochloride, Ivermectin, Fingolimod, Methylprednisolone, and Ritonavir (Li et al., 2020d; Wang et al., 2020c). Several antibodies have also been raised that inhibit or neutralize the virus. Scientist from Netherlands and Germany discovered human monoclonal antibody 47D11, which target a conserved epitope of the S1_B RBD domain (Wang et al., 2020d). B₃₈ is another monoclonal antibody that can block SARS-CoV-2 from binding to the ACE2 receptor (Collins, 2020). Israel Institute of Biological Science is associated with the development of a monoclonal antibody and a VSV-ΔG-spike vaccine (Bedi, 2020; Yahalom-Ronen et al., 2020). (List of vaccines under clinical trial developed by different Pharmaceutical Company is depicted in Table 1). Council of Scientific and Industrial Research (India) has received approval for the clinical trial of two drugs – Favipiravir and Phytopharmaceutical by the Drug Control General of India (DGCI) to combat coronavirus (*CSIR Receives Approval for Clinical Trial of Two Drugs, 'Phytopharmaceutical, and Favipiravir' to Treat COVID-*

Table 1

Status of vaccines and natural products by various institutes that have been considered for clinical trial against SARS-CoV-2.

	Vaccine candidate	Developer	Technology	Status	Origin	References
Western	EpiVacCorona	Vector Institute	The vaccine contains small portions of viral proteins, known as peptides	Approved for emergency use	Russia	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> 2020, <i>COVID-19 Vaccine Tracker</i> 2020
	mRNA-1273	Moderna, US National Institute of Allergy, and Infectious Diseases	Targets the spike protein of the COVID-19 virus	Approved for emergency use	United States	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Clinical Trial Number NCT04299724 for "Safety and Immunity of Covid-19 aAPC Vaccine"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	BNT162b2	BioNtech, FoSun Pharma, and Pfizer	RNA based vaccine	Approved for emergency use	Germany	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Clinical Trial Number NCT04368728 for "Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults"</i> , 2020, <i>Clinical Trial Number NCT04352608 for "Safety and Immunogenicity Study of 2019-nCoV Vaccine (Inactivated) for Prophylaxis SARS CoV-2 Infection (COVID-19)"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	Ad5-nCoV	CanSino Biologics, and Institute of Biotechnology of the Academy of Military Medical Science	Recombinant adenovirus type 5 vector (Ad5)	Approved for emergency use	China	Zimmer et al., 2020, Basta and Moodie, 2021, Liu, 2020, <i>Clinical Trial Number NCT04341389 for "A Phase II Clinical Trial to Evaluate the Recombinant Novel Coronavirus Vaccine (Adenovirus Vector)"</i> , 2020, <i>Clinical Trial Number NCT04313127 for "A Phase I Clinical Trial in 18–60 Adults"</i> , 2020, Pollard, 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	Gam-Covid-Vac/Sputnik V	Gamaleya Research Institute	Adenovirus (Ad5 and Ad26) vaccine	Approved for emergency use	Russia	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	Ad26.CO2. S	Janssen	Adenovirus viral vector vaccine	Approved for emergency use	Netherlands and Israel	Basta and Moodie, 2021
	AZD1222	Oxford/AstraZeneca	Adenovirus vector	Approved for emergency use	United Kingdom	Basta and Moodie, 2021
	Covishield	Serum Institute of India	Adenovirus vector	Approved for emergency use	India	Basta and Moodie, 2021
	Covaxin	Indian Council of Medical Research, National Institute of Virology, and Bharat Biotech	Based on an inactivated form of the coronavirus	Approved for emergency use	India	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	Inactivated (Vero cells)	Sinopharm, and Wuhan Institute of Biological Products	The vaccine contains viral proteins	Approved for emergency use	China, United Arab Emirates	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	BBIBP-CorV	Sinopharm	The vaccine contains viral proteins	Approved for emergency use	China	Basta and Moodie, 2021
	CoronaVac	Sinovac Biotech	Based on an inactivated form of the coronavirus	Approved for emergency use	China	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	UB-612	COVAXX	The vaccine contains parts of several viral proteins	Phase III	The United States of America	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
	NVX-CoV2373	Novavax	Recombinant nanoparticle technology to generate antigen derived from the coronavirus spike (S) protein and contains Novavax patented saponin-based Matrix-M™ adjuvant to enhance the	Phase III	The United States of America	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020

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Table 1 (continued)

Vaccine candidate	Developer	Technology	Status	Origin	References
RBD-Dimer	Anhui Zhifei Longcom, and the Chinese Academy of Medical Sciences	immune response and stimulate high levels of neutralizing antibodies Based on the RBD section of the spike protein of the coronavirus, along with an adjuvant	Phase III	China	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Medicago	Grow vaccines in a plant called <i>Nicotiana benthamiana</i> by delivering virus genes into the plant cells which create protein shells that mimic viruses	Phase III	Canada	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020, <i>COVID-19 Medicago Development Program</i> , 2021
AG0302-COVID19	Anges, Osaka University, and Takara Bio	DNA based vaccine	Phase III	Japan	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
INO-4800	Inovio Pharmaceuticals	By electroporation DNA plasmid vaccine delivered	Phase III	USA, South Korea	Zimmer et al., 2020, Liu, 2020, <i>Clinical Trial Number NCT04283461 for "Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
CVnCoV	CureVac	mRNA	Phase III	Germany	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
BNT162b1	BioNtech, FoSun Pharma, and Pfizer	RNA based vaccine	Phase III	Germany	Zimmer et al., 2020, <i>Clinical Trial Number NCT04368728 for "Study to Describe the Safety, Tolerability, Immunogenicity, and Potential Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Adults"</i> , 2020, <i>Clinical Trial Number NCT04352608 for "Safety and Immunogenicity Study of 2019-nCoV Vaccine (Inactivated) for Prophylaxis SARS CoV-2 Infection (COVID-19)"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
SCB-2019	Clover Biopharmaceuticals, GSK, and Dynavax	Based on spike proteins of coronavirus	Phase III	China, The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
SNG001	Synairgen	Inhaled formulation of Interferon-beta-1a to the lungs directly via nebulisation which controls body's antiviral response	Phase III	United Kingdom	Zimmer et al., 2020, Basta and Moodie, 2021, Thanh et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
BRACE	Murdoch Children's Research Institute	The vaccine was developed in the early 1900s for the protection against tuberculosis	Phase III	Australia	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Remdesivir (GS-5734)	Gilead Science	Inhibit RNA dependent RNA Polymerase	Phase III	The United States of America	Zimmer et al., 2020, Wang et al., 2020c, Rees, 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
QazCovid-in Soberana 1	Kazakhstan RIBSP Finlay Vaccine Institute	Inactivated The vaccine contains RBD, along with proteins from bacteria and aluminum hydroxide	Phase III Phase II-III	Kazakhstan Cuba	Basta and Moodie, 2021 Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
ChAdOx1 nCoV-19	University of Oxford	Adenovirus vector	Phase II-III	United Kingdom	Zimmer et al., 2020, <i>Clinical Trial Number NCT04324606 for "A Study of a Candidate COVID-19 Vaccine (COV001)"</i> , 2020, European Union Clinical Trials Register, 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
ZyCoV-D	Zyudus Cadila	DNA based vaccine delivered by skin patch	Phase II	India	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
GX-19	Genexine	DNA based vaccine	Phase II	South Korea	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
BNT162a1	BioNtech, FoSun Pharma, and Pfizer	RNA based vaccine	Phase II	Germany	Basta and Moodie, 2021

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Table 1 (continued)

Vaccine candidate	Developer	Technology	Status	Origin	References
BNT162b3	BioNtech, FoSun Pharma, and Pfizer	RNA based vaccine	Phase II	Germany	Basta and Moodie, 2021
BNT162c2	BioNtech, FoSun Pharma, and Pfizer	RNA based vaccine	Phase II	Germany	Basta and Moodie, 2021
Sf 9 cells	West China Hospital of Sichuan University	A vaccine made from the RBD region of the spike protein	Phase II	China	Zimmer et al., 2020, Basta and Moodie, 2021, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
S-268019	Shionogi	The vaccine contains parts of several viral proteins	Phase II	Japan	Basta and Moodie, 2021
ChulaCov19	Chulalongkorn University, and Chula Vaccine Research Center	mRNA based vaccine	Phase II	Thailand	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
COVID-eVAX Unnamed	Takis Institute of Medical Biology	DNA based vaccine Based on an inactivated form of the coronavirus	Phase II Phase II	Italy China	Basta and Moodie, 2021 Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Sanofi, and GSK	Based on viral proteins that produced the proteins with engineered viruses that grow inside insect cells	Phase II	French	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
GBP510	SK Bioscience Co Ltd	The vaccine contains parts of several viral proteins	Phase II	South Korea	Basta and Moodie, 2021
DeINS1-2019-nCoV-RBD-OPT	University of Hong Kong, Beijing Wantai Biological Pharmacy, and Xiamen University	The vaccine produces part of the coronavirus spike protein	Phase II	China	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
AV-COVID-19	Aivita Biomedical Inc.	Based on replicating viral vector	Phase II	United States of America	Basta and Moodie, 2021
Nanocovax	Nanogen	The vaccine contains parts of several viral proteins	Phase II	Vietnam	Basta and Moodie, 2021
NDV-HXO-S IIBR-100	Mahidol University Israel Institute for Biological Research	Based on replicating viral vector Based on replicating viral vector	Phase II Phase II	Thailand Israel	Basta and Moodie, 2021 Basta and Moodie, 2021
AdCLD-CoV19 AKS-452	Cellid Co University Medical Centre GroningenUnU	Based on replicating viral vector The vaccine contains parts of several viral proteins	Phase II Phase II	South Korea Netherlands	Basta and Moodie, 2021 Basta and Moodie, 2021
MVC-COV1901	Medigen, and Dynavax	Contain a combination of spike proteins and an adjuvant	Phase II	Taiwan and Vietnam	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
COVAC 2	University of Saskatchewan	The vaccine contains parts of several viral proteins	Phase II	Canada	Basta and Moodie, 2021
KBP-201	Kentucky BioProcessing	Grow vaccines in a plant called <i>Nicotiana benthamiana</i> by delivering virus genes into the plant cells which create viral protein	Phase II	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
FINLAY-FR-1	Instituto Finlay de Vacunas Cuba	The vaccine contains parts of several viral proteins	Phase II	Cuba	Basta and Moodie, 2021
CIGB-669	Centre for Genetic Engineering and Biotechnology	The vaccine contains parts of several viral proteins	Phase II	Cuba	Basta and Moodie, 2021
CIGB-66	Centre for Genetic Engineering and Biotechnology	The vaccine contains parts of several viral proteins	Phase II	Cuba	Basta and Moodie, 2021
BECOV2A	Biological E Limited	The vaccine contains parts of several viral proteins	Phase II	India	Basta and Moodie, 2021
BECOV2B	Biological E Limited	The vaccine contains parts of several viral proteins	Phase II	India	Basta and Moodie, 2021
BECOV2C	Biological E Limited	The vaccine contains parts of several viral proteins	Phase II	India	Basta and Moodie, 2021
BECOV2D	Biological E Limited	The vaccine contains parts of several viral proteins	Phase II	India	Basta and Moodie, 2021
TAK-019	TAKEDA	The vaccine contains parts of several viral proteins	Phase II	Japan	Basta and Moodie, 2021
TAK-919	TAKEDA	RNA based vaccine	Phase II	Japan	Basta and Moodie, 2021
Covigenix VAX-001	Entos Pharmaceuticals	DNA based vaccine	Phase II	Canada	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
RBD SARS-CoV-2 HBsAg VLP	SpyBiotech	Contains a mixture of proteins which also contain spike protein of coronavirus	Phase II	United Kingdom	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
ARCT-021	Aracturus Therapeutics, and Duke-NUS Medical School	mRNA based vaccine	Phase II	Singapore	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020

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Table 1 (continued)

Vaccine candidate	Developer	Technology	Status	Origin	References
LV-SMENP-DC	Shenzhen Geno-Immune Medical Institute	Lentiviral minigene vaccine	Phase II	China	Zimmer et al., 2020, Liu, 2020, <i>Clinical Trial Number NCT04334980 for "Evaluating the Safety, Tolerability and Immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
AG0301-COVID19	Anges, Osaka University, and Takara Bio	DNA based vaccine	Phase II	Japan	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
GLS-5310 Sars-CoV2-Vaccine (Vero Cells)	GeneOne Life Science Inc. Minhai Biotechnology Co	DNA based vaccine Inactivated	Phase II Phase II	South Korea China	Basta and Moodie, 2021 Basta and Moodie, 2021
VLA2001	Valneva	Inactivated	Phase I-II	United Kingdom	Basta and Moodie, 2021
Unnamed	Baylor College of Medicine, Texas Children's Hospital, Biological E, and Dynavax	Based on viral proteins	Phase I-II	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Sinovac Biotech	Inactivated	Phase I-II	China	Zimmer et al., 2020, <i>IVI, INOVIO, and KNIH to Partner With CEPI in a Phase I/II Clinical Trial of INOVIO's COVID-19 DNA Vaccine in South Korea</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Chumakov Center	Based on an inactivated form of the coronavirus	Phase I-II	Russia	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
V591	Merck Sharp and Dohme Corp.	Based on replicating viral vector	Phase I-II	Austria, Belgium, United States of America	Basta and Moodie, 2021
Unnamed	University of Tübingen	The vaccine contains viral proteins along with an immune-stimulating adjuvant	Phase I	Germany	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Sovereign 2	Finlay Vaccine Institute	The vaccine contains RBD part of spike protein fuse with tetanus vaccine	Phase I	Cuba	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
NBP2001 QazCovid	SK Bioscience Co Ltd Research Institute for Biological Safety Problems	The vaccine contains viral protein Based on an inactivated form of the coronavirus	Phase I Phase I	South Korea Kazakhstan	Basta and Moodie, 2021 Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Shenzhen Kangtai Biological Products	Based on an inactivated form of the coronavirus	Phase I	China	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Erciyes University	Based on an inactivated form of the coronavirus	Phase I	Turkey	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
CodaVax	Codagenix Inc.	Live-attenuated vaccine	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Razi Cov Pars	Ravi Vaccine and Serum Research Institute	The vaccine contains viral protein	Phase I	Iran	Basta and Moodie, 2021
FINLAY-FR-2	Instituto Finlay de Vacunas Cuba	The vaccine contains parts of several viral proteins	Phase I	Cuba	Basta and Moodie, 2021
Sclamp	University of Queensland, and CSL	Based on viral proteins	Phase I	Australia	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
COVIGEN COVAX-19	University of Sydney Vaxine	DNA based vaccine Based on viral proteins	Phase I Phase I	Australia Australia	Basta and Moodie, 2021 Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
CoVac-1 AdimrSC-2f	Tuebingen Adimmune	Based on viral proteins The vaccine contains the RBD section of the virus's spike protein	Phase I Phase I	Germany Taiwan	Basta and Moodie, 2021 Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
GRAd-COV2	ReiThera, and Lazzaro Spallanzani National Institute for Infectious Diseases in Rome	Based on an adenovirus that infects gorillas	Phase I	Rome	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
VXA-CoV2-1	Vaxart	Adenovirus 5 (Ad5) vaccine	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020

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Table 1 (continued)

Vaccine candidate	Developer	Technology	Status	Origin	References
Unnamed	Themis Bioscience, Merck, and Institut Pasteur	The vaccine uses a weakened measles virus that carries a gene for the coronavirus spike protein.	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Merck, and IAVI	Based on vesicular stomatitis viruses	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	German Center for Infection Research	The vaccine carries the gene for the spike protein	Phase I	Germany	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
hAd5-Covid-19	ImmunityBio Inc.	The vaccine uses the Ad5 adenovirus	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Brilife	Israel Institute for Biological Research	Based on vesicular stomatitis viruses	Phase I	Israel	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	City of Hope	Based on a weakened form of a virus called Modified Vaccinia Ankara contain two coronavirus genes to the virus — one for the spike protein, and one for another protein called nucleocapsid	Phase I	The United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
ARCoV1	Academy of Military Medical Sciences, Suzhou Abogen Biosciences, and Walvax Biotechnology	mRNA based vaccine	Phase I	China	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
CORVax12	Oncosec Immunotherapies	DNA based vaccine encodes spike protein and IL-12 (Signaling molecule that enhances the immune system's ability to make antibodies to the spike protein)	Phase I	United States of America	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Unnamed	Beijing Institute of Biological Products, and Wuhan Institute of Biological Products	The vaccine contains an inactivated virus	Phase I	China	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
bac TRL-Spike	Symvivo Corporation, University of British Columbia, and Dalhousie University	DNA, bacterium medium	Phase I	Canada	Zimmer et al., 2020, <i>Clinical Trial Number ChiCTR2000031809 for "A Randomized, Double-Blind, Placebo Parallel-Controlled Phase I/II Clinical Trial for Inactivated Novel Coronavirus Pneumonia Vaccine (Vero Cells)"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
Covid-19/aAPC	Shenzhen Geno-Immune Medical Institute	Lentiviral Vector, pathogen-specific artificial antigen-presenting dendritic cells	Phase I	China	Zimmer et al., 2020, Liu, 2020, <i>Clinical Trial Number NCT04276896 for "Immunity and Safety of Covid-19 Synthetic Minigene Vaccine"</i> , 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
PTX-COVID19-B	Providence Therapeutics Holding Inc.	RNA based vaccine	Phase I	Canada	Basta and Moodie, 2021
LNP-nCoVsaRNA	Imperial College of London	RNA based vaccine	Phase I	United Kingdom	Zimmer et al., 2020, <i>Draft Landscape of COVID-19 Candidate Vaccines</i> , 2020, <i>COVID-19 Vaccine Tracker</i> , 2020
CoV2 SAM (LNP)	GlaxoSmithKline	RNA based vaccine	Phase I	United States of America	Basta and Moodie, 2021
AdCOVID	Altimmune Inc.	Based on non-replicating viral vector	Phase I	United States of America	Basta and Moodie, 2021
MVA-SARS-2-S	Universitätsklinikum Hamburg-Eppendorf	Based on non-replicating viral vector	Phase I	Germany	Basta and Moodie, 2021
BBV154	Bharat Biotech	Based on non-replicating viral vector	Phase I	India	Basta and Moodie, 2021
COH04S1	City of Hope Medical Centre	Based on replicating viral vector	Phase I	United States of America	Basta and Moodie, 2021
ERUCOV-VAC	Health Institutes of Turkey	Inactivated	Phase I	Turkey	Basta and Moodie, 2021
Unnamed	Shifa Pharmed Industrial Co	Inactivated	Phase I	Iran	Basta and Moodie, 2021
V590	Merck Sharp and Dohme Corp.	Based on replicating viral vector	Phase I	United States of America	Basta and Moodie, 2021
COVID-19-101	Institut Pasteur	Based on replicating viral vector	Phase I	Belgium, France	Basta and Moodie, 2021

Product	Developer	Possible mechanism of action	Status	Origin	References
Natural				Singapore	

(continued on next page)

Table 1 (continued)

Product	Developer	Possible mechanism of action	Status	Origin	References
Lianhua Qingwen	Nanyang Technological University	Anti-inflammatory, Reduce viral load	Phase III		Runfeng et al., 2020, <i>Clinical Trial Number NCT04433013 for "A Randomized Controlled Trial Assessing the Efficacy of Lianhua Qingwen as an Adjuvant Treatment in Patients With Mild Symptoms of COVID-19"</i> , 2020
Natural Honey	Misir University of Science and Technology	Antiviral	Phase III	Egypt	Kumari et al., 2020, <i>Clinical Trial Number NCT04323345 for "Efficacy of Natural Honey Treatment With Novel Coronavirus"</i> , 2020
Honey and <i>Nigella sativa</i>	Federal Postgraduate Medical Institute	Antiviral, Immunomodulation	Phase III	Pakistan	Kumari et al., 2020, <i>Clinical Trial Number NCT04347382 for "Honey and Nigella sativa Trial Against COVID-19 (HNS-COVID-PK)"</i> , 2020
Traditional Chinese Medicine	Xiyuan Hospital of China Academy of Chinese Medical Sciences	Decrease level of cytokines, resist lung inflammation	Phase III	China	Clinical Trial Number NCT04323332 for "Traditional Chinese Medicine for Severe COVID-19", 2020
Pectin and <i>Acacia Senegal</i> (Gum Arabic)	Al-Neelain University	Changes of the level of Tumor Necrosis Factor (TNF), interleukin IL8,IL6,IL10 and decrease viral load	Phase III/II	Sudan	<i>Clinical Trial Number NCT04381871 for "Potential role of Gum Arabic as Immunomodulatory Agent Among COVID 19 Patients (GA and COVID19)"</i> , 2020
Açaí palm berry extract	University Health Network, Toronto and University of Toronto	Inhibition of Nod like receptor family, pyrin-containing 3 (NLRP3)	Phase II	Canada	<i>Clinical Trial Number NCT04404218 for "The Acai Berry COVID-19 Anti-Inflammation Trail (ACAD)"</i> , 2020
ArtemiC	MGC Pharmaceutical LTD	Antimicrobial	Phase II	Australia	Kumari et al., 2020, <i>Clinical Trial Number NCT04382040 for "A phase II, Controlled Clinical Study Designed to Evaluate the Effect of ArtemiC in Patients Diagnosed With COVID-19"</i> , 2020
<i>Nigella sativa</i>	King Abdulaziz University	Antiviral	Phase II	Saudi Arabia	Kumari et al., 2020, <i>Clinical Trial Number NCT04401202 for "Effects of Nigella sativa as a Treatment of Patients With Upper Respiratory Tract Infection Caused by SARS-Coronavirus-2: A Prospective, Randomized, Open-label, Controlled Clinical Study"</i> , 2020

19, 2020). A group of scientists of Israel also discover antibodies (REGN10933, REGN10934, REGN10987, REGN10989) which together can act against the spike protein (Barum et al., 2020).

8.2. Homeopathy

Homeopathic medicines are being considered for the treatment of COVID-19 in a few countries, including many Indian states. Arsenic album is regarded as an immune booster by Central Council for Research in Homeopathy (Kumar, 2020a). The world-first clinical trial of Homeopathic medicine *Bryonia alba* 200 for the treatment of COVID-19 has begun at Neminath Homeopathic Medical College, Agra (India). During the initial trial, *Bryonia alba*-200 was regularly provided to 42 patients, and within 5–7 days, the test results were found to be negative for 40 patients. Further studies for its effectiveness are still in progress (Kumar, 2020b; Kumar, 2020a). Cuba, a North American country also declared about the distribution of Prevegovir, a new homeopathic immunological booster (Torres, 2020). In Hong Kong, a study was performed with 18 COVID-19 patients who had a variety of symptoms. Patients treated with *Bryonia alba* 30C recovered 20% in the first 12 h and 70–95% on day 3, patients treated with *Gelsemium sempervirens* 30C recovered 20–50% in the first 12 h and 70–100% on day 3, patients treated with Arsenicum album 30C recovered 50% in the first 12 h and 100% on day 3, and patients treated with Eupatoriu 30C recovered 50% in the first 12 h and 100% on day 3 (To and Fok, 2020). In Italy, 50 patients were treated with medicines namely Arsenicum Album, Phosphorus Flavius, *Atropa belladonna*, Antimonium Tartaricum, *Eupatorium perfoliatum*, Hepar Sulphur, *Lycopodium clavatum*, Kaliumphosphoricum which showed overall recovery and no patients were needed to be hospitalized during the recovery period (Valeri, 2020). Despite the fact that many homeopathic medicines showed promising results in COVID-19 patients, this branch of medicine is understudied in terms of efficacy and needs further research.

8.3. Traditional

Traditional medicine was successfully used in China for treatment of

approximately 58.3% of the cases (Clinical Trial Number NCT04283461 for "Safety and Immunogenicity Study of 2019-nCoV Vaccine (mRNA-1273) for Prophylaxis SARS CoV-2 Infection", 2020; Clinical Trial Number NCT04299724 for "Safety and Immunity of Covid-19 aAPC Vaccine", 2020). Shanghai Institute of Materia Medica and Wuhan Institute of Virology found Shuanghuanglian to be promising in inhibiting SARS-CoV-2 3CL protease and the replication of SARS-CoV-2 in Vero E6 cells. Baicalin and baicalein, two known compounds present in Shuanghuanglian showed inhibitory effect against the protease (Wang et al., 2020a; Wang et al., 2020c; Keech et al., 2020). Moreover, Lianhuaqingwen capsule, which is known for its anti-inflammatory activity and a regulator of immune responses to clear viral load. A clinical trial was started to study its efficiency against SARS-CoV-2 which is currently in Phase-3 (Runfeng et al., 2020; Clinical Trial Number NCT04433013 for "A Randomized Controlled Trail Assessing the Efficacy of Lianhua Qingwen as an Adjuvant Treatment in Patients With Mild Symptoms of COVID-19", 2020). Yupingfeng San, a cocktail of three herbs namely Astragalus, Fangfeng, and Atractylodes was found to improve immune responses (Keech et al., 2020). Sangjuyin and Yinqiao san are other two Chinese traditional medicines that are reported to be used in lung heat clearance and cough relief (Keech et al., 2020). Qingfei paidu decoction shows an efficiency of 90% against COVID-19 symptoms. It was found to enhance immune responses and inhibit duplication of the SARS-CoV-2 genome by blocking ribosomal proteins (Baum et al., 2020). A group of Scientist further mentioned few Chinese traditional remedies which include Qingfei Paidu Tang, Xiang Sha Liu Junzi Tang, Shen Ling Baizhu San, Qingfei Paidu Tang, Qingwen Baidu Yin, Shen Fu Tang, Ma Xing Shi Gan Tang, Da Yuan Yin, Xia Ling Tang which are used in China to deal with COVID-19 but their efficiency against the virus still awaits detailed study (Ren et al., 2020; Li et al., 2020e). India also had a great treasure of traditional knowledge in medical science, well-known as Ayurveda. In Chennai, a patient treated with Sudarsana Churna, Talisadi Churna with honey, and Dhanwantara Gutika was observed to recover on 16th day and tested negative on 33th day (Girija and Sivan, 2020). The Indian Health Ministry (Ministry of Health and Family Welfare) recently stated that the Council of Scientific and Industrial Research (CSIR), India under the guidance of The Indian Council of Medical Research (ICMR), New

Delhi have started conducting clinical trials for traditional Ayurvedic medicines like Ashwagandha, Guduchi Pippali, Ayush-64, and Yashtimadhu (Xu and Zhang, 2020; Nanigia, 2020). Recently, Thailand Health Ministry have approved *Andrographis paniculata* for the treatment of COVID-19 patients (Yujejwattana, 2020). (Status of the natural products that have been considered for clinical trial against SARS-CoV-2 is described in Table 1) This branch of science is also relatively less investigated towards effectiveness to COVID-19 and demands a detailed and thorough study.

8.4. Innovative prevention strategies against COVID-19

Dealing with the COVID-19 outbreak is of high concern and from the initial stage of the onset of these pandemic, researchers, high-tech manufacturers, designers came forward with innovative equipment for the prevention of the SARS-CoV-2 virus. PPEs like masks, gloves, and other essentials like rapid testing facilities, ventilators are needed in extraordinary quantities especially for the frontline coronavirus warriors. Chinese company based Anti-virus snood, smart helmet, 3D printed isolation wards, drones; Italian company based 3D printed ventilator valves; South Korean based coronavirus booth; Czech based 3D printed face shield (Wainwright, 2020); Indian company based cost-effective novel mask (*500 Membrane Based Face-Masks Made by CSMCRI Were Given for User Trial and Feedback to Indian Red Cross Society, Bhavnagar Branch on 23.04.2020, 2020*), bag valve mask ventilator (Ambu bag) by Mahindra and Mahindra Company, DRDO based UV disinfection tower (*DRDO Develops WiFi-Enabled UV Disinfection Tower, 2020*), mobile virology research lab and diagnostic laboratory (*MMVRDL, 2020*), portable or fixed microwave sterilizer – ATULYA (Siddiqui, 2020), IIT based incubation boxes (Sharma, 2020) to name a few are being designed for prevention and surveillance of COVID-19 outbreak.

9. Emerging strategies for COVID-19

In a sea of different platforms for the possible treatment of COVID-19, CRISPR-Cas mediated gene-editing technology remains promising which can be used to manipulate target genes using guide RNA and Cas protein (cleavage protein) (Hu et al., 2014; Kaminski et al., 2016; Wang et al., 2016). Gene knockout was successfully employed in coronaviruses using CRISPR technology (Chekani-Azar et al., 2020; Abbott et al., 2020). With advances in detection and identification of more Cas13 target sites in human infectious coronaviruses, CRISPR-Cas13 can be programmed with updated RNA sequences (Freiji et al., 2019). Delivery of CRISPR-Cas into the target RNA in a living individual could be using lipid nanoparticles (Sago et al., 2018), HEDGES platform (Handumrongkul et al., 2019), or ribonucleoprotein complex (Amirkhanov and Stepanov, 2019) but is still challenging. The Cas13d can be harnessed to target a wide range of ssRNA viruses including SARS-CoV-2 along with CARVER (Cas13-assisted restriction of viral expression and readout) for rapid diagnostics and anti-viral drug development (Sago et al., 2018). Besides this molecular platform, nanotechnology-based (silver and gold-based) therapy (Kerry et al., 2019; Lara et al., 2010; Vijayakumar and Ganesan, 2010; Ahmed et al., 2016; Sportelli et al., 2020), ultrashort pulsed laser irradiation technology using short-lived reactive oxygen species (singlet oxygen) (Tsen et al., 2014; Kingsley et al., 2018), and ultrasound-based therapy (Lichtenstein and Malbrain, 2017) could be employed in the medicament of COVID-19. Although these emerging techniques are under development, extensive research, and laboratory diagnosis with proper validation are prerequisite to bringing into play in combating COVID-19. Plasma therapy (convalescent) into infected patients may be of clinical benefit (Mair-Jenkins et al., 2015; Luke et al., 2006). Recently, the FDA has passed a few guidelines recommending medical professionals and researchers on the administration and study of investigational COVID-19 convalescent plasma (*Recommendations for Investigational COVID-19 Convalescent Plasma, 2020*). Llama derived antibodies called VHH and bacterial super glue to form specific

multimeric VHH with potential antiviral activity (Hultberg et al., 2011; Schreur et al., 2020). This novel approach opens up new opportunities to optimize, reformate, and validate novel tools. Another promising treatment that may regenerate lung disease and reduce inflammation due to COVID-19 infection could be the use of stem cells. This very recent research approach is under trial while waiting for its validation (Chrzanowski et al., 2020).

10. Challenges in pandemic diseases

A major challenge in answering to emerging pandemic diseases is that vaccines may not extant or effectual against them. Each new strain requires a novel vaccine. It requires several months to years to design and mass-produce a safe and effective vaccine. Moreover, in emergency and severe illness difficulties may arise during transport and storage, vaccine security, maintenance of low temperature may become compromised. Besides, meeting supply-demand, distribution, and uptake of vaccines where vaccination is commonly not practiced are the significant challenges that the government may face during emerging pandemic diseases.

Of note, many of the highlighted specifics in the review are in the developmental or experimental stage which requires clinical validation and some specifics may change with increasing data and more studies on COVID-19.

11. Update and summary

Synthetic DNA of SARS-CoV-2 have been cloned into yeast-based platform and reverse genetics maybe use to through light into the functional molecular biology and pathogenesis of emerging viruses including SARS-CoV-2 (Thao et al., 2020). Genomic sequence was used for identifying novel drug targets against COVID-19 through viral-human protein interaction analysis and then cheminformatic analysis of existing compounds was carried resulting in the identification of 66 human proteins that can be drug gable (Gorden et al., 2020). The new SARS-CoV-2 outbreak has brought out many outstanding research work and studies. It includes understanding its infections, transmission, history, genome, and employment of previously reported drugs and many clinical trials with a single goal of designing a drug/vaccine to help our immune system fight better. Information regarding molecular function and structure of the viral proteins has helped greatly in the detection and evolution of new potent and efficient medicines. The rapid increase of information about SARS-CoV-2 along with highly sensitive and reproducible diagnostic and proper obeying of health authority's awareness and guidelines should bring about control of COVID-19 soon.

CRediT authorship contribution statement

Ankur Das: Conceptualization, Original draft preparation, data curing, and writing.

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Khaleda Begum: Writing, validation.

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Declaration of competing interest

The authors declare that no competing interest exists.

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